Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Hepatitis B Virus Infection (Last updated April 22, 2015; last reviewed April 22, 2015)

Epidemiology

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide.[1,2] Globally and in North America, approximately 10% of HIV-infected patients have evidence of chronic HBV infection.[3-5]

In countries with a low prevalence of endemic chronic HBV infection, the virus is transmitted primarily through sexual contact and injection drug use, whereas perinatal and early childhood exposures are responsible for most HBV transmission in higher prevalence regions.[1,2,6] Although the general modes of transmission are similar to HIV, HBV is transmitted more efficiently than HIV.[1,2] HBV has an average incubation period of 90 days (range 60–150 days) from exposure to onset of jaundice and 60 days (range 40–90 days) from exposure to onset of abnormal liver enzymes. Genotypes of HBV (A–H) have been identified with different geographic distributions. Genotype A is most common among patients in North America and Western Europe.

Clinical Manifestations

Acute infection is usually asymptomatic. When they manifest, symptoms may include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice. Most patients with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue, until they develop cirrhosis and signs of portal hypertension (i.e., ascites, variceal bleeding, coagulopathy, jaundice, or hepatic encephalopathy). Hepatocellular carcinoma (HCC) is asymptomatic in its early stages and usually, but not always, occurs in the setting of HBV - or hepatitis C (HCV)-related cirrhosis.

Diagnosis

All HIV-infected patients should be tested for HBV infection because of shared routes of transmission. Initial testing should include serologic testing for surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B surface antibody (anti-HBs). In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure and anti-HBc immunoglobulin M is usually detectable at the onset of symptoms.

Chronic HBV infection is defined as persistent HBsAg detected on 2 occasions at least 6 months apart. Patients with chronic HBV infection should be further tested for HBV e-antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. Active disease, which can be HBeAg-negative or HBeAG-positive, can be distinguished from inactive disease by the presence of serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevation. Patients whose past infection has resolved are HBsAg-negative with positive anti-HBs and anti-HBc, although cccDNA may remain in hepatocyte nuclei. Seroreversion may occur (becoming serum HBsAg-positive again) under severe immune suppression, as is seen with rituximab therapy or after stem cell transplant.[7,8]

The presence of anti-HBc alone, often occurs on testing as an isolated anti-HBc test result, usually signifies infection with HBV in the past with subsequent loss of anti-HBs. It occurs in 6.6% to 58.6% of HIV-infected patients,[9-11] Incidence of HBV viremia in HIV-infected patients with the isolated anti-HBc pattern ranges from 1% to 36%.[10,12-15] The clinical significance of isolated anti-HBc is unknown[16-18,20] but it may indicate chronic or, more likely, resolved infection in HIV-infected individuals.[16,17,21] In a low-prevalence country such as the United States, isolated anti-HBc may also represent a false-positive result.[16-19] HIV-infected patients have a higher frequency of isolated anti-HBc, particularly those with underlying HCV coinfection.[19,22,23]

Diagnosis of Disease Progression and the Role of Assessment of Liver Fibrosis

Compared with HIV-uninfected individuals, those who are HIV-infected have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[24] In HBV-monoinfected individuals, HBV DNA suppression, anti-HBe seroconversion (to anti-HBe-seronegativity), HBsAg loss, and acquisition of anti-HBs are all associated with a decreased incidence of cirrhosis, HCC,[25-27] and improved survival.[28-31] In comparison, the predictive value of these parameters in persons with HIV/HBV coinfection indicate they usually are more likely to have detectable HBeAg,[24,32] lower rates of seroconversion to anti-HBe, and increased risk of HCC, liver-related mortality and morbidity.[33,34]

HBV infection can result in a dynamic disease with a number of phases that are associated with either active or inactive chronic hepatitis. Duration of disease phases is different in those who acquire infection as neonates and young children compared with those who acquire infection as adults. Adults do not have an "immune-tolerant" phase (high levels of HBV DNA and low or rising ALT levels). Clinicians should be knowledgeable about these phases for HBV-monoinfected patients to determine who needs treatment and who should be monitored. In HIV/HBV coinfection, monitoring and treatment are also focused on the simultaneous treatment of both viruses.

HBV-monoinfected patients who are HBeAg-seropositive usually have high HBV DNA levels (>20,000 IU/mL) and abnormal ALT levels. However, with perinatal infection or infection acquired in early childhood, patients initially have an immune tolerance phase, with the presence of HBeAg, normal ALT levels, and high levels of HBV DNA but minimal or no liver disease. These patients may develop HBeAg-positive chronic hepatitis B with elevated ALT levels and remain at risk for HCC, cirrhosis, and flares of HBV.[35]

Anti-HBe seroconversion usually implies a transition from active disease to an inactive carrier state.[35] This transition can be spontaneous or associated with effective HBV treatment. In some instances, increased levels of ALT may precede a decline in HBV DNA that is accompanied by anti-HBe seroconversionp, that is, loss of HBeAg and development of anti-HBe. However, such spontaneous HBeAg conversion rates in HIV-infected patients appear to be lower than in monoinfected patients. The inactive chronic HBV state is characterized by a negative HBeAg, normal ALT levels, and an HBV DNA level <2,000 IU/mL. Patients in the inactive state remain at risk of reactivation of HBV and development of HCC, but the risk is lower than for individuals with active HBV replication. In any patient, the re-emergence of abnormal liver enzyme tests may reflect HBeAg-negative chronic HBV disease, a result of mutations in the basal core and precore promoter regions. Although levels of HBV DNA are usually lower, HBeAg-negative patients experience an unrelenting but fluctuating course of disease progression, with fluctuating HBV DNA levels.[35] Thus, even in a patient without HBeAg, serum ALT and HBV DNA levels still should be monitored.

Patients diagnosed with chronic HBV infection should have a complete blood count, ALT, aspartate aminotransferase (AST), albumin and bilirubin levels, and prothrombin time monitored at baseline and every 6 months thereafter to assess severity and progression of liver disease. Patients with chronic HBV are at increased risk of HCC and imaging studies every 6 months are recommended in those who are cirrhotic, Asian male and older than age 40, Asian female and older than age 50, or male older than age 20 and from sub-Saharan Africa, as individuals in all of these groups are at increased risk of disease progression.[35]

Persistent low-level serum ALT abnormalities may be associated with significant liver disease, although normal ALT levels also may be seen in the setting of cirrhosis. Transient or persistent elevations in serum ALT levels can occur before loss of HBeAg, on discontinuation of anti-HBV therapy, and in association with emergence of HBV drug resistance.

Assessment of stage of liver fibrosis is important to know when to initiate esophageal variceal and HCC screening in cirrhotic patients. Fibrosis stage can be determined by liver biopsy or by noninvasive methods such as transient elastography, The decision to perform a liver biopsy should be individualized, especially given Department of Health and Human Services recommendations to initiate antiretroviral therapy (ART)-containing anti-HBV drugs regardless of CD4 T lymphocyte (CD4) cell count in HIV/HBV coinfected

patients.[36] There is increasing evidence that noninvasive methods (i.e., elastometry and serum biochemical indices) to evaluate liver fibrosis can be used to determine fibrosis in HBV.37-40 For example, one study demonstrated that transient elastography was able to discriminate moderate to severe fibrosis from mild fibrosis in HIV/HBV coinfection.[41]

Preventing Exposure

HBV is primarily transmitted by percutaneous or mucosal exposure to infectious blood or body fluids. Therefore, HIV-infected patients should be counseled about transmission risks for HBV and avoidance of behaviors associated with such transmission **(AIII)**. Such counseling should emphasize sexual transmission as well as the risks associated with sharing needles and syringes, tattooing or body-piercing.

Preventing Disease

All household members and sexual contacts of patients with HBV should be screened and all susceptible contacts should receive both hepatitis A (HAV) and HBV vaccines regardless of whether they are HIV-infected **(AII)**. HBV immunization is the most effective way to prevent HBV infection and its consequences. All HIV-infected patients without chronic HBV or immunity to HBV should be vaccinated with HBV vaccine **(AII)** or with the combined HAV and HBV vaccine **(AII)**. This is of special importance in patients with high-risk behaviors associated with HBV infection and not on cART containing HBV-active drugs.[42] All non-immune patients should be tested annually for both anti-HBs (immunity to HBV) and HBsAg (for infection).

Prevaccination screening should include HBsAg, anti-HBs, and anti-HBc. A patient who is seropositive for anti-HBc and anti-HBs has resolved infection and does not need vaccination. Similarly, the presence of anti-HBs alone at levels >10 IU/mL is consistent with seroprotection, usually from vaccination,[43] and no further vaccinations are required. The interpretation is less clear in individuals with isolated anti-HBc. Aside from false-positive results, this pattern may signify infection in the distant past with subsequent loss of anti-HBs.[44] Most HIV-infected patients with isolated anti-HBc are HBV DNA-negative and not immune to HBV infection. They should be vaccinated with a complete series of HBV vaccine followed by anti-HBs testing **(BII)**.[23,45]

The magnitude and duration of immunogenicity to HBV vaccination in HIV-infected adults is significantly lower than in HIV-seronegative healthy adults.[46-49] Factors associated with poor response to vaccine include low CD4 cell counts,[47,50-55] presence of detectable HIV RNA,[51,55,56] coinfection with HCV, occult HBV infection (a rare situation of unclear clinical significance), and the general health status of the host.[15,23,57-61] Based on these data, early vaccination is recommended in HIV-infected patients before CD4 cell counts decline to <350 cells/mm^3 **(AII)**. However, in patients who present to care at a lower CD4 cell count, vaccination should not be deferred until CD4 counts increase to >350 cells/mm^3 because some HIV-infected patients with CD4 counts <200 cells/mm^3 do respond to vaccination **(AII)**. Given decreased vaccine responses among HIV-infected patients compared to HIV-uninfected individuals, anti-HBs titers should be obtained 1 month after completion of the vaccine series. For patients with anti-HBs levels <10 IU/mL, a second vaccine series is recommended **(BIII)**, although some specialists might delay revaccination until after a sustained increase in CD4 cell count is achieved on ART **(CIII)**. Two randomised controlled trials have shown that using four doses of double-dose vaccine produces higher anti-HBs titers than 3 doses of standard-dose vaccine,[62,63] and one study also showed a higher overall response rate.[63] Some specialists consider this approach—four vaccinations—improves immunologic response in HIV-infected individuals either as an initial vaccination schedule or in patients who are non-responders **(BI)**. However, whether a schedule of four double-dose vaccines is superior to 4 single-dose or 3 double-dose vaccines is still unclear. Another study suggested that HIV-infected patients with CD4 counts >350 cells/mm^3 had improved responses when vaccinated with a double-dose vaccine on a 0-, 1-, and 6-month schedule.[50] Although other approaches have been investigated to improve responses, such as the use of combined hepatitis A and B vaccine,[64,65] or the use

of adjuvants;66 data are insufficient to support a broad recommendation for these approaches at this time. While additional studies are needed to determine optimal vaccination strategies in patients with advanced immunosuppression, the vaccination series for HBV should be initiated at first visit regardless of CD4 cell count.[67]

HAV vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease, are men who have sex with men, or who are injection drug users **(AIII)**. Responses to the HAV vaccine are reduced in HIV-infected patients with CD4 counts <200 cells/mm^3.[68,69] Antibody response should be assessed 1 month after vaccination is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm^3 **(BIII)**.

Patients with chronic HBV disease should be advised to avoid alcohol consumption **(AIII)**.

Treating Disease

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV monoinfection: to prevent disease progression and to reduce HBV-related morbidity and mortality. To this end, treatment for HBV is intertwined with that for HIV.

Special Considerations with Regard to Starting ART

Regardless of CD4 cell count or need for HBV treatment, ART that includes agents with activity against both HIV and HBV is recommended for all patients coinfected with HIV and HBV. **(AII)**. For HIV/HBV coinfected individuals, ART MUST include two drugs active against HBV, preferably tenofovir and emtricitabine, regardless of the level of HBV DNA **(AIII)**. Such a regimen will reduce the likelihood of immune reconstitution inflammatory syndrome (IRIS) against HBV and reduce risk of resistance that could occur with newer regimens such as with abacavir/lamivudine backbone.

If the patient refuses ART there are few options that can be used for treatment of HBV alone. Directly acting HBV drugs must not be given in the absence of a fully suppressive ART regimen. This is because most drugs active against HBV also are active against HIV (anti-HBV drugs such as tenofovir, entecavir, emtricitabine, lamivudine, adefovir, and possibly telbivudine), but when given without more potent anti-HIV agents, can produce drug-resistant HIV in the recipient **(AII)**. Alternative HBV therapy for patients who refuse initiation of ART would be 48 weeks of pegylated interferon (IFN) (see below).

The Department of Health and Human Services guidelines for treatment of HIV infection recommend the fixed-dose coformulation of tenofovir/emtricitabine or abacavir/lamivudine as recommended nucleoside reverse transcriptase inhibitor (NRTI) backbones for ART-naive patients.[36] Because both tenofovir and emtricitabine have anti-HBV activity, it is also the treatment of choice for HIV/HBV coinfected patients **(AIII)**. Tenofovir is active against wild-type and lamivudine-resistant HBV strains. Studies in HBV/HIV-coinfected patients (most of them carrying lamivudine-resistant HBV) have shown, on average, 4 $\log_{10}$ declines in HBV DNA levels.[70-75] Tenofovir has a high genetic barrier for development of resistance mutations. However, the nephrotoxicity associated with tenofovir may limit its use in some patients. In patients who have renal dysfunction or are at high risk of developing renal dysfunction, entecavir can be added to a fully suppressive ART regimen **(BIII)**. Chronic administration of lamivudine or emtricitabine as the only active drug against HBV **should be avoided** because of the high rate of selection of HBV drug-resistance mutations **(AI)**.

Most patients receiving ART should continue HBV therapy indefinitely **(CIII)** because relapses after response occur, particularly in those with lower CD4 cell counts, and because discontinuation of nucleos(t)ide analogue therapy is associated with a HBV flare in approximately 30% of cases,[76,77] with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.[47,78-80] If anti-HBV therapy and ART must be discontinued, transaminase levels should be monitored every 6 weeks for 3 months and every 3 to 6 months thereafter. If a flare occurs, anti-HBV therapy and ART should be

reinstituted and can be potentially lifesaving **(AIII)**.

Alternative Treatment of HBV in HIV-Infected Patients Who Are Not Receiving ART

In general, HBV and HIV co-treatment is recommended. But if ART cannot be given or the patient refuses HIV treatment or is a long-term non-progressor, treatment for active HBV disease is indicated.[35] Specifically, anti-HBV therapy is indicated for individuals with elevated ALT and elevated HBV DNA >2,000 IU/mL or significant fibrosis **(AI)**.[35] All patients with advanced liver disease or cirrhosis should also be treated. Additional information on HBV treatment indications is found in the American Association for the Study of Liver Diseases (AASLD) guidelines.[35]

For HIV/HBV-coinfected patients not receiving ART who meet criteria for HBV therapy as described above, pegylated interferon-alfa-2a alone might be considered and is the only option that will not predispose to antiretroviral (ARV) drug resistance in HIV when used in the absence of ART **(CIII)**. Adefovir alone is of limited value in this setting because it is less potent and has a higher risk of selecting for resistance mutations than the preferred HBV nucleos(t)ides.[35] However, data are limited on the use of these agents alone in the HIV/HBV-coinfected population. Patients who are HBeAg-positive, infected with HBV genotype A, in the early stages of liver disease, and have high ALT levels are the most likely to benefit from pegylated IFN- alfa **(CIII)**, which requires a defined course of 48 weeks. Tenofovir, entecavir, lamivudine, emtricitabine, and telbivudine **should not be used** in the absence of ART because of the development of HIV-resistance mutations.[81,82] If there is no indication for HBV treatment, continued monitoring and reassessment of risk of liver-related morbidity and mortality is required because HBV is a dynamic disease that can change with time.

Some HIV/HBV-coinfected patients also have chronic HCV infection. There is scant information on the treatment of HBV/HCV/HIV coinfection. Because patients with HBV, HCV, and HIV appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,[83-85] attempts should be made to treat both hepatitis viruses, if feasible. If ART is administered, then anti-HBV therapy must be included as part of the regimen (as above) and anti-HCV therapy can be introduced as needed (see Hepatitis C Infection) **(CIII)**. If ART is not desired, IFN-alfa-based therapy, which has activity against both HCV and HBV, should be considered **(CIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

In order to prevent emergence of drug-resistant variants and evaluate response for patients on nucleos(t)ide analogues, treatment response should be monitored by testing for HBV DNA at 12-week intervals. HBeAg also should be tested every 6 to12 months in patients who are HBeAg-positive. Treatment responses are defined as follows:

- Primary non-response is an HBV DNA <1 $\log_{10}$ decline at 12 weeks.[86]
- A complete virologic response is an undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.[86]
- A partial virologic response is ≥1 $\log_{10}$ decline but still detectable HBV DNA at Week 24.[86]
- A maintained virologic response is a response that continues while on therapy, and a sustained virologic response is one that is still present 6 months after stopping therapy.

For patients who are HBeAg-positive, loss of HBeAg is also a measure of virologic response. Other markers that indicate treatment success include improvement in liver histology based on biopsy or noninvasive markers, normalization of serum aminotransferases, and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response; however, this desirable serologic response is uncommon.[35]

Major toxicities of IFN-alfa (pegylated or standard) are flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and psychiatric reactions including depression, insomnia, irritability, anxiety. Other common reactions are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

Nucleos(t)ide analogs: Renal toxicity with tenofovir, including increased serum creatinine or renal tubular dysfunction, has been observed; both are more frequent in HIV-infected patients with underlying renal insufficiency, older patients or those treated for prolonged periods.[87] These biochemical changes are usually reversible on discontinuation of tenofovir.

Electrolytes and serum creatinine levels should be evaluated at baseline and every 3 to 6 months, and urinalysis every 6 months. Because renal toxicity may be reversible, alternative anti-HBV therapy should be used if renal toxicity occurs **(AI)**. If tenofovir is used in patients with baseline renal insufficiency, dose adjustment as noted in the package insert is required.

Entecavir-associated lactic acidosis is uncommon but has been reported in HBV-monoinfected patients with advanced cirrhosis.[88] Telbivudine can cause creatine phosphokinase (CPK) elevations >7 times the upper limit of normal, with some reports of myopathy.[89] Thus, CPK should be measured at baseline, every 3 to 6 months, and if musculoskeletal symptoms develop. If CPK levels are elevated, telbivudine should be discontinued and replaced with another anti-HBV agent **(AI)**.

Adefovir causes renal tubular disease at doses of 30 mg/day or higher, but this toxicity is uncommon at the recommended 10 mg/day dose. In HBV-monoinfected patients, incidence of increased creatinine levels with 5 years of adefovir therapy ranges from 3% to 8%.[90,91]

Immune Reconstitution Inflammatory Syndrome (IRIS)

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so called "hepatitis flare",[92] which constitutes IRIS in HIV/HBV-coinfected persons. IRIS may be manifested by dramatic increases in serum aminotransferase levels as CD4 cell counts rise within the first 6 to 12 weeks after starting ART, with signs and symptoms characteristic of acute hepatitis. After introduction of ART, serum ALT levels should be monitored closely; some experts recommend ALT testing at 6 and 12 weeks, then every 3 to 6 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated International Normalized Ratio and low serum albumin) should prompt consultation with a hepatologist.

Flares are worse in patients with more severe liver disease, especially in those with cirrhosis.[93] Distinguishing between ARV-associated hepatotoxicity or other causes of hepatitis (acute hepatitis A, C, D or E virus, Epstein-Barr virus, herpes simplex virus, cytomegalovirus) and IRIS may be difficult. ARV-associated hepatotoxicity may be dose-dependent or idiosyncratic. The risk of hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases (ALT, aspartate aminotransferase) and the presence of HBV or HCV coinfection before initiation of ART.[94-101] However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80%–90%) coinfected patients do not have hepatotoxicity,[97] and clinically significant hepatotoxicity (elevated direct bilirubin) is rare; aminotransferase levels return to baseline in most cases, even if the offending medication is continued.[95,102] Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless patients have symptoms of hypersensitivity (e.g., fever, lymphadenopathy, rash), symptomatic hepatitis (i.e., nausea, vomiting, abdominal pain, or jaundice), or elevations in serum aminotransferase levels >10 times the upper limit of normal. However, the development of jaundice is associated with severe morbidity and mortality and the offending drug(s) should be discontinued **(AIII)**.[103]

The major problem in managing ALT flares is distinguishing between drug-induced liver injury and HBV reactivation, IRIS, emergence of drug resistance, and HBeAg seroconversion. In drug-induced liver toxicity, determining the offending medication also can be challenging. A review of the medication history and testing for serum HBV DNA, HBeAg, HIV RNA levels, and CD4 cell count can help distinguish between these possibilities. Liver histology also may help to differentiate drug toxicity (e.g., increased eosinophils) from viral hepatitis (e.g., portal inflammation). If the flare is severe or HBV drug resistance is suspected, then consultation with a hepatologist is recommended. Other causes of abnormal liver tests should be sought,

including use of drugs or alcohol, other viral hepatitis infections (hepatitis A, C, D, and E), and nonalcoholic fatty liver disease.

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogues is defined as primary nonresponse after 12 weeks of therapy in patients who consistently adhere to HBV therapy or an increase in HBV DNA levels greater than 1 $\log_{10}$ above nadir. In either situation, treatment failure is generally due either to drug-resistant HBV if on lamivudine/emtricitabine monotherapy or noncompliance. If drug-resistant HBV is present, a change in treatment needs to be made **(AII)**. Distinct resistance patterns exist with the different groups of anti-HBV drugs: the L-nucleosides (telbivudine, lamivudine, emtricitabine); acyclic phosphonates/nucleotides (adefovir and tenofovir); and D-cyclopentane (entecavir), which shares some resistance mutations with the L-nucleosides. Many experts will obtain HBV-resistance testing because it has value in distinguishing between noncompliance and resistance, evaluating patients with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir. However, tenofovir has not been associated with clinical resistance, although slow response has been noted as discussed above. Addition of entecavir has led to suppression of HBV DNA in these slow-to-respond patients.[104]

Lamivudine (or emtricitabine) monotherapy for HBV leads to emergence of drug-resistant HBV increasingly with time on treatment and **should not be used** as the sole anti-HBV drug in an ART regimen **(AII)**. The rate of development of lamivudine resistance is approximately 20% per year in HIV/HBV-coinfected patients treated with lamivudine alone.[105] If lamivudine resistance is suspected or documented, tenofovir should be added **(BIII)**.[106-108] Because patients with lamivudine-resistant HBV will have cross-resistance to the other L-nucleosides (telbivudine, emtricitabine), and partial resistance to entecavir, those agents **should not be used** in patients found to have lamivudine-resistant HBV **(AI)**.[109] All nucleoside analogs must be dose adjusted for renal insufficiency per package insert guidelines and Table 8.

If treatment failure occurs on entecavir, then the only rational choice is replacement with tenofovir (+/- emtricitabine) because of the cross resistance that occurs with L-nucleosides (telbivudine, lamivudine, emtricitabine) **(AI)**.

Patients whose HBV initially fails to respond to pegylated IFN-alfa can be given nucleos(t)ide analogue therapy following the recommendations previously described **(CIII)**.

If treatment failure with tenofovir occurs, particularly in lamivudine- or emtricitabine-experienced patients, then entecavir may be an active alternative, especially if higher doses of entecavir can be used **(CIII)**. However, documented *in vivo* resistance to tenofovir has not yet been reported. Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly in patients who are receiving an HBV drug, with high potency and a high genetic barrier to resistance, such as tenofovir, but they may still be detectable for some years. Thus, in a compliant patient with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels **(BII)**. Improvement of response with the addition of entecavir has been reported, but whether such "intensification therapy" is required is unclear. Nonetheless, patients on drugs that are less potent or that have a lower barrier to resistance, such as adefovir or L-nucleosides, who have partial virologic responses (<2 $\log_{10}$ drop in HBV DNA levels from baseline at 24 weeks) should be switched to a more potent regimen such as tenofovir with emtricitabine or entecavir (if treatment-naive) because of the risk of development of drug resistance to the intial therapy **(BII)**.

Special considerations for treating end-stage liver disease

Treatment of end-stage liver disease in HIV/HBV-coinfected patients should be managed as it is in HIV-seronegative patients. These patients should be referred to a hepatologist. As with monoinfected patients, IFN-alfa is **contraindicated** in end-stage liver disease **(AI)**, but nucleoside analogs are safe and efficacious **(AI)**.[105,110,111] All patients with ascites should undergo paracentesis to exclude spontaneous bacterial

peritonitis (SBP).[112] Management of ascites includes sodium restriction (<2 g/day) and the recommended diuretic regimen is spironolactone combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone) **(AI)**. All patients who have had SBP and those with ascites total protein <1 g/dL should receive prophylaxis against SBP with administration of oral antibiotics such as norfloxacin (400 mg/day), ciprofloxacin 750 mg/week or trimethoprim-sulfamethoxazole (one double-strength tablet/day) **(AI)**.[113]

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all patients with cirrhosis at the time of diagnosis and then every 1 to 2 years to identify substantial gastroesophageal varices (see American Association for the Study of Liver Diseases guidelines). Patients with varices require non-selective beta blockers, such as nadolol or propranolol, that are the mainstay of both primary and secondary prevention of variceal hemorrhage. Esophageal variceal banding is another preventive option, particularly for those who cannot tolerate beta blockers. Hepatic encephalopathy is treated with a 40-g protein diet and the use of non-absorbable disaccharides such as lactulose and/or non-absorbable antibiotics such as rifaximin.

Patients with HBV-related cirrhosis are at increased risk of HCC[114] and should be screened every 6 to 12 months with imaging studies, as recommended in HBV monoinfection. Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center and whether the patient has cirrhosis. Usually ultrasound is the initial preferred imaging modality. HCC can occur without cirrhosis and HIV coinfection appears to increase the risk of HCC in HBV,[115] but more frequent screening in HIV/HBV coinfection has not been studied, and so is not recommended. HIV/HBV-coinfected patients with decompensated liver disease and/or early HCC are candidates for orthotopic liver transplantation. HIV infection is not a contraindication to organ transplantation with the use of effective ART.[116] Because transplantation does not cure HBV infection, post-transplant hepatitis B immune globulin (HBIG) and HBV treatment is required **(AII)**.

Preventing Recurrence

As previously indicated, most patients should continue HBV therapy (with the exception of pegylated IFN) indefinitely **(CIII)** because relapses after response occur, particularly in those with lower CD4 cell counts, and because reports of hepatitis flares after discontinuation of lamivudine in those who have not reached treatment endpoints can be extrapolated to other HBV-active drugs.[78-80]

Special Considerations During Pregnancy

Pregnant women, including HIV-infected women, should be screened for HBsAg, anti-HBc, and anti-HBs. Those who are HBsAg- and anti-HBs-negative should be offered vaccination against HBV. Treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk of pre-term labor and delivery may be increased with acute HBV infection.

High maternal HBV DNA levels correlate strongly with perinatal HBV transmission, including failures of HBV passive-active immunoprophylaxis.[117-120] Although a high viral load is clearly important, it is not the only factor predisposing to prophylaxis failure, as demonstrated by a case report in which perinatal HBV transmission occurred despite suppression of HBV DNA to undetectable levels in the mother with antepartum lamivudine and appropriate immunoprophylaxis of the infant.[121,122]

ART including drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection, including pregnant women, who require HBV treatment or who are initiating ART for their own health. Because combination ART is recommended for all HIV-infected women during pregnancy to prevent perinatal transmission of HIV, even if it is not required for their own health, all HIV/HBV-coinfected pregnant women should receive an ART regimen containing HBV-active drugs. This is because of concern about potential IRIS-related flare of HBV activity after initiation of ART, even in women with relatively high CD4 cell counts, if drugs without anti-HBV activity are used. In addition, using drugs with anti-HBV activity

during pregnancy will lower HBV levels and decrease the risk that HBIG and HBV vaccine will fail to prevent perinatal transmission of HBV. Following delivery, considerations regarding the continuation of ARV drugs in mothers are the same as in other adults who are not pregnant. Therefore, once HBV therapy with nucleos(t)ide analogs is initiated, treatment is recommended to be continued indefinitely. However, if ARV drugs are discontinued postpartum, frequent monitoring of liver function tests for potential HBV flare is recommended, with prompt reinitiation of treatment for both HIV and HBV, should a flare occur.

Tenofovir given in combination with lamivudine or emtricitabine, is the preferred dual-NRTI backbone for pregnant women with chronic HBV infection **(AIII)**, as it is in nonpregnant HIV/HBV-coinfected individuals.[124] Because emtricitabine, lamivudine, and tenofovir have activity against both HIV and HBV, the recommended dual-NRTI backbone for HIV/HBV-coinfected individuals who are not pregnant is tenofovir/emtricitabine or tenofovir/lamivudine **(AI)**. Of the ARV agents with activity against hepatitis B, the one used most often in pregnancy is lamivudine. As of July 2013, more than 4,000 cases of pregnancy outcomes after first-trimester exposure to lamivudine have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure.[123] Lamivudine has been well tolerated by pregnant women and is a recommended NRTI for use in pregnancy **(AII)**.[124] Similarly, no increase in birth defects has been noted in 1400 cases of first-trimester exposure to emtricitabine, which is an alternative NRTI for use in pregnancy (http://www.apregistry.com) **(BII)**.[123] Tenofovir was not teratogenic in animals, but at high doses, reversible bone changes were seen in multiple animal species. A total of 1,982 cases of first-trimester exposure to tenofovir have been reported to the Antiretroviral Pregnancy Registry with no increase in birth defects noted.[123]

Several other ARV agents with activity against HBV, including adefovir and telbivudine, have been evaluated and found not to be teratogenic in animals, but experience in the first trimester with these agents in human pregnancy is limited. These drugs could be included in a regimen during pregnancy if other options are inappropriate. Each of these agents should be administered only in combination with a fully suppressive ARV regimen because of the risk of development of ARV drug resistance. Entecavir was associated with skeletal anomalies in rats and rabbits, but only at high, maternally-toxic doses. Data on use of entecavir and adefovir in human pregnancy are not available. Telbivudine was given to 95 HBV-seropositive, HIV-seronegative women during the third trimester in one study, and it was well tolerated with no birth defects observed. Cases of exposure during pregnancy to any of the ARV and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com).

IFN-alfa formulations are not recommended for use in pregnancy. Although these agents are not teratogenic, they are abortifacient at high doses in monkeys and **should not be used** in pregnant women because of their direct antigrowth and antiproliferative effects **(AII)**.[125]

Infants born to HBsAg-positive women should receive HBIG and HBV vaccine within 12 hours of delivery **(AI)**. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively.

Infants born to HBsAg-positive women should receive hepatitis B immune globulin and hepatitis B vaccine within 12 hours of delivery **(AI)**. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively.

Recommendations for Preventing and Treating Hepatitis B Virus (HBV) Infection (page 1 of 2)

Preventing HBV Infection

Indications for HBV Vaccination:

- Patients without chronic HBV infection or without immunity to HBV (anti-HBs <10 IU/mL) **(AII)**
- Patients with isolated anti-HBc and with negative HBV DNA **(BII)**.
- Early vaccination is recommended before CD4 count falls below 350 cells/mm^3 **(AII)**, as low CD4 count at time of vaccination has been associated with poor response to the vaccine.
- However, in a patient with low baseline CD4 cell count, vaccination should not be deferred until CD4 reaches >350 cells/mm^3, as some patients with CD4 <200 cells/mm3 do respond to vaccination **(AII)**.

Vaccination Schedule:

- HBV vaccine IM (Engerix-B® 20 mcg/mL or Recombivax HB® 10 mcg/mL) at 0, 1, and 6 months **(AII)**; or
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2 and 6 months **(BI)**; or
- Combined HAV and HBV vaccine (Twinrix®) 1 mL IM as a 3-dose series (at 0, 1, and 6 months) or as a 4-dose series (at days 0, 7, 21 to 30, and 12 months) (**AII)**
- Anti-HBs should be obtained 1 month after completion of the vaccine series, anti-HBs <10 IU/mL will be considered as non-responders. **(BIII)**

For Vaccine Non-Responders:

- Revaccinate with a second vaccine series **(BIII)**
- For patients with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a sustained increase in CD4 count with ART **(CIII)**.

Alternative Vaccine Dose for Non-Responders:

- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2 and 6 months **(BI)**,

Treating HBV Infection

Indication for Therapy:

- All HIV/HBV coinfected patients, regardless of CD4 count (AII). Treatment should be used for both HIV and HBV infections **(AIII)**.

Preferred Therapy:

- The ART regimen must include 2 drugs active against HBV, preferably with tenofovir 300 mg + emtricitabine 200 mg (or lamivudine 300 mg) PO once daily **(AIII)**.

Duration of Therapy:

- Most patients on treatment for HBV and HIV will receive therapy indefinitely **(CIII)**.

Alternative Therapy

If ART cannot be given or if the patient refuses ART, or is a HIV long-term non-progressor:

- Anti-HBV therapy is indicated for elevated ALT, and HBV DNA >2,000 IU/mL, significant liver fibrosis, advanced liver disease or cirrhosis **(AI)**.
- Peg-IFN-alfa 2a 180 mcg SQ once weekly for 48 weeks **(CIII)**, *or*
- Peg-IFN- alfa 2b 1.5 mcg/kg SQ once weekly for 48 weeks **(CIII)**

If tenofovir cannot be used as part of the ART regimen because of current or high risk of renal dysfunction:

- A fully suppressive ART regimen without tenofovir should be used, with the addition of entecavir to the regimen **(BIII)**

Note: Chronic administration of emtricitabine or lamivudine monotherapy for HBV infection **should be avoided** in most cases due to high rate of selection of HBV drug resistance mutation **(AI)**.

Other Considerations:

- HAV vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease, are men who have sex with men, or who are injection drug users **(AIII)**
- Antibody responses to HAV should be assessed 1 month after completion of vaccination series. If HAV Ab IgG is negative, patients should be revaccinated when the CD4 count is >200 cells/mm^3 **(BIII)**.
- Directly acting HBV drugs (such as tenofovir, entecavir, emtricitabine, lamivudine, adefovir, and possibly telbivudine) must not be given in the absence of a fully suppressive ART regimen to avoid selection of drug resistant HIV **(AI)**.
- As patients with HBV/HCV/HIV coinfection appear to have accelerated liver fibrosis progression, high risk of HCC, and increased mortality, treatment for both HBV and HCV infection should be initiated, if feasible.
- When changing ART regimens, it is crucial to continue agents with anti-HBV activity **(BIII)**.
- If anti-HBV therapy must be discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3-6 months thereafter.
- If a hepatic flare occurs after drug discontinuation, HBV therapy should be re-instituted, as it can be potentially life saving **(AIII)**.

Key to Acronyms: ab = antibody; anti-HBs = hepatitis B surface antibody; ALT = alanine transferease; ART = antiretroviral therapy; CD4 = CD4 T-lymphocyte cell; HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; IgG = immunoglobulin; IM = intramuscular; PO = orally; SQ = subcutaneous

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